

Remarks

The claimed invention

The claimed adjustable threshold switch comprises a first regulatory gene (R1) that is expressed from a first, inducible promoter (P1), and a second regulatory gene (R2) that is expressed from a second promoter (P2), that is active in the absence of a repressor. A product of the first regulatory gene inhibits or reduces (represses) expression of the second regulatory gene, and a product of the second regulatory gene inhibits or reduces (represses) expression of the first regulatory gene. (p. 2, line 30 – p. 3, line 5).

Transcription of the first gene encoding the first repressor protein is inducible by an activating agent. The activating agent induces transcription from the inducible promoter by a mechanism other than inhibiting expression or activity of the second repressor and is required for activity of the inducible promoter (p. 3, lines 7-12, and p. 11, lines 19-23).

In a default first expression state, the second promoter (P2) is active, and the inducible promoter (P1) is inactive, due to the absence of a sufficient amount of the activating agent and the inhibitory effect of the second regulatory gene product. Addition of the activating agent activates the inducible promoter (P1) and switches the adjustable threshold switch to a second expression state in which the inducible promoter (P1) is active and the second promoter (P2) is substantially inactive (p. 3, lines 7-12).

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 11, 14, and 15 as being directed to non-statutory subject matter. In particular, the Examiner asserts that claims 11, 14, and 15 can reasonably read to encompass a human cell in a human body, or even a human. While not conceding the correctness of the Examiner's position, claim 11 has been amended to include the term "isolated", as suggested by the Examiner, with the understanding that "isolated" shall mean that the host cell is not an integral part of a human body. Claims 14 and 15 depend from claim 11 and therefore incorporate this limitation. Claim 12 has been amended to depend from claim 1.

Rejections under 35 U.S.C. § 102

Claims 1-7 and 10-15 stand rejected under 35 U.S.C. § 102 as being anticipated

by Bailey, et al., hereinafter “Bailey”. Applicants respectfully traverse the rejection and have amended claim 1 to more clearly point out features of the claimed invention that distinguish it from Bailey. In particular, claim 1 has been amended to recite that the activating agent induces transcription from the inducible promoter by a mechanism other than inhibiting expression or activity of the second repressor. Support for the amendment is found at p.7, lines 15-23 of the specification, where the activating agents of the instant claims are contrasted with the “switching agents” suitable for use in a bistable toggle switch such as those described in copending application 09/872,868. Amended claim 1 also recites that the activating agent is required for activity of the inducible promoter, i.e., in the absence of a sufficient concentration of the activating agent the inducible promoter is substantially inactive. Support for the amendment is found at p. 7, lines 16-18, and elsewhere in the specification. Applicants submit that amended claim 1 is not anticipated by Bailey, as described further below.

Bailey teaches dual operon constructs that comprise two repressors, R and R2, under control of two promoters, wherein R2 controls (represses) transcription of the structural gene that encodes R, and R controls (represses) transcription of the structural gene that encodes R2 (col. 6, lines 19-28). The operon that encodes R2 also contains a sequence that encodes a product of interest. The constructs of Bailey allow one to maintain cells in a state in which transcription from the first operon, which includes both the structural gene encoding R2 and the sequence that encodes a product of interest is repressed by a repressor (R) transcribed from the second operon. Bailey further teaches that expression of the product of interest can be induced by addition of an inducer.

Applicants submit that the constructs described by Bailey do not include an inducible promoter from which transcription is activated by an inducer that acts by a mechanism other than inhibiting expression or activity of a repressor that would otherwise repress transcription from the promoter, as required by claim 1 as amended. Instead, the inducers taught by Bailey function by binding to a repressor, thereby preventing the repressor from binding to its operator (col. 3, lines 5-7, and col. 4, lines 65-68). Bailey teaches that suppression of expression by a repressor can be reversed by reducing the concentration of the repressor or by neutralizing the repressor with an inducer (col. 4, line 67 – col. 5, line 3). Bailey does not describe inducers that activate

expression by other mechanisms. Furthermore, the promoters of Bailey do not require an activating agent for activity. Instead, they are active in the absence of a repressor (i.e., they are constitutive), and, if repressed, become active when the effect of the repressor is removed (col. 4, lines 11-13).

The inducible promoters of the instant claims are distinct from those taught by Bailey. In particular, inducible promoters suitable for use in the claimed invention are capable of being activated by an activating agent and of being suppressed by a repressor (p. 8, lines 14-19). Examples of suitable inducible promoters and corresponding activating agents are listed in Table 1 (p. 9). The promoters exemplified in the constructs of Bailey, on the other hand, are found instead in Table 2 (p. 10) of the instant application, which lists “constitutive” promoters (i.e., promoters active in the absence of a repressor). Such promoters are suitable for use as the second promoter in the adjustable threshold switch, but not for use as the inducible promoter. Thus Applicants submit that the invention of claim 1 (and claims dependent on it) is distinct from the constructs of Bailey and that Bailey therefore cannot anticipate the claimed invention. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 8 and 9 stand rejected under 35 U.S.C. § 103 as being unpatentable over Bailey, et al. The Examiner applies Bailey as in the rejections under 35 U.S.C. § 102 and asserts that it would have been obvious to modify the systems taught by Bailey to include a second sequence of interest operatively linked to the operon that does not already contain a sequence of interest. Applicants submit that, as described above, Bailey does not anticipate the adjustable threshold switch of claim 1. Therefore, even if motivation to modify Bailey to include a second sequence of interest operatively linked to the operon that does not already comprise a sequence of interest existed, and even if there was a reasonable that doing so would successfully allow one to regulate expression of more than one gene product and obtain the second gene product in a controlled manner, as asserted by the Examiner, Applicants submit that resulting system would not meet the limitations of claims 8 and 9. In particular, the resulting system would not comprise an inducible promoter that is activatable by an activating agent that induces transcription

from the inducible promoter by a mechanism other than inhibiting expression or activity of the second repressor and is required for activity of the inducible promoter, as recited in claim 1, from which claims 8 and 9 depend. Instead, the system would comprise two constitutive promoters that are active in the absence of a repressor and do not require an activating agent for activity. As described in MPEP §706.02(j) and in *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), one of the requirements to establish a *prima facie* case of obviousness is that the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicants submit that this requirement has not been met. Withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 1-15 stand rejected as being unpatentable over claims 1-16 of copending Application No. 09/872,868. The Examiner states that the adjustable threshold switch is regulatable by the absence/presence of the two repressors. Applicants submit that this statement is not a fully accurate characterization of the instantly claimed invention, as described above. In particular, while the first and second repressors do repress the second and first (inducible) repressors, respectively, in accordance with the claimed invention, an activating agent induces transcription from the inducible promoter by a mechanism other than inhibiting expression or activity of the second repressor and is required for activity of the inducible promoter. Thus even in the absence of the second repressor, the inducible promoter is substantially inactive, whereas in the presence of the activating agent transcription from the inducible promoter is activated even in the presence of the second repressor, as described above. Thus the expression state of the adjustable threshold switch is regulated primarily by the activating agent. When the activating agent is present at or above a threshold concentration, transcription from the inducible promoter is active, while if the activating agent is not present at a sufficient concentration, transcription from the inducible promoter is substantially inactive, allowing transcription from the other promoter to be active.

In contrast, the claims of the '868 application require first and second promoters that are active in the absence of a repressor. The promoters therefore do not require presence of an activating agent in order to be active as is the case for the inducible promoters of the instantly claimed invention. Activity of the promoters in the '868

application is repressed in the presence of a corresponding repressor, and this repression can be relieved by a switching agent. However, the switching agents of the '868 application are distinct from the activating agents of the instant claims since the latter induce transcription by a mechanism other than inhibiting expression or activity of the repressor.

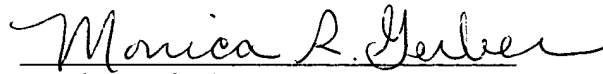
In summary, Applicants submit that the claims of the '868 application are not specific embodiments of the instant claims since neither of the promoters of the '868 claims is induced by an activating agent that induces transcription by a mechanism other than inhibiting expression or activity of the repressor, and the promoters of the '868 claims do not require an activating agent for activity. The distinction between the inducible promoters and activators of the instant application and the promoters and switching agents suitable for use in the invention of the '868 claims is further evident from a comparison of Table 1 (p. 9) of the instant application, with the promoters and switching agents of Table 1 (p. 27) of the '868 application. It is noted that none of the promoters appears in both tables. Thus Applicants submit that the claims of the '868 application define a different and separately patentable invention. Withdrawal of the rejection is respectfully requested.

In light of the foregoing Amendment and Remarks, Applicants respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful or if questions arise regarding the amendment proposed above, please do not hesitate to contact the undersigned at (617) 248-5071.

Please charge any fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,

A handwritten signature in cursive script, reading "Monica R. Gerber".

Monica R. Gerber, M.D., Ph.D.

Registration Number 46,724

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Dated: May 5, 2004.
3694261_1.DOC